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(57) Abstract

Novel multi–binding compounds are disclosed that modulate enzymatic processes. The compounds of the invention comprise from 2–10 ligands covalently connected, each of said ligands being capable of binding to an enzyme, enzyme substrate or enzyme cofactor thereby modulating the biological processes/functions thereof.

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NOVEL THERAPEUTIC AGENTS THAT MODULATE ENZYMATIC PROCESSES
NOUVEAUX AGENTS THERAPEUTIQUES MODULANT LES PROCESSUS ENZYMATIQUES
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English Abstract
Novel multi-binding compounds are disclosed that modulate enzymatic processes. The compounds of the invention comprise from 2-10 ligands covalently connected, each of said ligands being capable of binding to an enzyme, enzyme substrate or enzyme cofactor thereby modulating the biological processes/functions thereof.

French Abstract
L'invention porte sur de nouveaux composes multi-liants modulant les processus enzymatiques. Lesdits composes comportent de 2-10 ligands unis par covalence dont chacun peut se fixer a une enzyme, a un substrat d'enzyme ou a un cofacteur d'enzyme et modifier par la leurs processus et fonctions biologiques.

Fulltext Availability:
Detailed Description
Claims

Detailed Description
... effects.
Other examples of diseases in which enzymes are involved include infectious diseases caused by **bacteria** , protozoa or fungi, viral diseases such as AIDS (e.g., reverse transcriptase or protease enzymes... rasagiline, 1370U, L-650477, indeloxazine,
Alzheimer's disease moclobemide, brofaromine, EXP-631
Neurodegenerative disease
Dementia
Dihydrofolate reductase Cancer Methotrexate., edattexate. piritrexim, LY LY-316373, (1 1.3) Psoriasis 1954U89, E-34335, AG...tumor
Uterine cervix tumor
Bladder tumor
Urinary tract tumor
Renal tumor
17
Ribosomal protein biosynthesis **Bacterial** infection Chloramphenicol, erythromicin, clarithromycin, azithromycin, (50S ribosomal subunit) Pneurnocystis carinii infection dirithromycin, flurithromycin clindamycin, lincomycin **bacteria**] Tetracycline, chlortetracycline, oxytetracycline, demeclocycline, (Aminoacyl tRNA site on 30S

methacycline, doxycycline, minocycline, CL-331002, ribosomal...

...CL-331928, CL-344667, CL-329998, PAM-MINQ
(2 2.12)
Ribosomal protein biosynthesis Anti- **bacterial** Streptomycin, gentamicin, tobramycin, amikacin, netilimicin, (30S subunit) kanamycin, neomycin, spectinomycin, dactimicin, paromomycin,
(2 2.12) trospectornycin
Ribosomal protein biosynthesis Anti- **bacterial** Fusidic acid, purpuromycin
(soluble protein factors)
(2 2.12)
Glucan synthase Fungal infection LY-303366...

...H)-one,
COP-5241 1. RG-8803, BP SU-6668
Beta subunit of DNA-dependant **Bacterial** infection Rifampin. rifabutin, rifalazil, T9, SPA-S-565
RNA polymerase
(2 7.6)
DNA polymerase...A-502 I 1. SPV-30, VF-1 618, TNK-651
19
D,D-transpeptidases **Bacterial** infection Beta-lactams
(PBP 2a.- 2b) Penicillin G, penicillin V, methicillin. nakillin. oxacillin.
cloxacillin, dicloxacillin...

...meziocillin, piperacillin,
(PBP 1a) cephalothin, cefazolin, cephalexin. cefadroxil, cefamandole, cefoxitin, cefaclor, cefuroxime, loracarbefcefonicid,
D,D- **Carboxypeptidase** cefotetan, ceforanide. cefotaxime. cefpodoximc proxetil,
(PBP 3-7) ceftizoxime, ceftriaxone, ccfopcrazone, ceftazidime, cefepime,
(3 16...CH-263, marimastat analogs
(3 24) Inflammatory bowel disease
Rheumatoid arthritis
Ulcerative colitis
Beta-Lactamase **Bacterial** infections Clavulanic acid, sulbactam. tazobactam. Ro 0480, HM-3030, (3 2.6) GD40, Ro48-8724...

...186195, DWC-751,2085-P, CP
72436, BK-218, BRL42715, SB-223328, Ro 1317
Undecaprenyidiphosphatase **Bacterial** infections Bacitracin
(3 1.27)
H+/K+ ATPase Peptic ulcer Omeprazole, leminoprazole, rabeprazole, egualen, SKF...
...34655, Ro 5364, T-776, nicotinamide
Gastrointestinal disease derivatives, pantoprazole, lansoprazole, SKF-96067, SPI-1447,
Bacterial infection AD-9161, YJA-20379, A-28200, SKF-96356, YM-020,
Fungal infection bafilornycin A derivatives, atractylon, saviprazole, OPC-22575
Parasite infection
Isomerase Enzymes
21
DNA gyrase **Bacterial** infections Nalidixic acid. norfloxacin, ofloxacin, ciprofloxacin, cinoxacin, (5 1.3)- Fungal infections sparfloxacin, lomefloxacin, fleroxacin...NSAIDs) including aspirin, indomethacin, ibuprofen, and naproxen. A fourth example of an oxidoreductase enzyme is **dihydrofolate reductase** (DHFR), which catalyzes the conversion of dihydrofolate polyglutamate to tetrahydrofolate polyglutamate ...is selectively inhibited by the antibacterial agent rifampin. In a third example, protein biosynthesis in **bacterial** cells is selectively inhibited by a variety of antibiotics (including gentamicin and other aminoglycosides, tetracycline...

...transglycosylase responsible for the glycosyl transferase reaction which incorporates lipid intermediate 11 into the growing **bacterial** cell wall. Vancomycin acts via a substrate sequestration mechanism; i.e., it binds to and...

...the action of a series of penicillin binding proteins (PBPs), most notably multiftmctional, membrane-bound **transpeptidase** enzymes that are responsible for cross-linking of the **bacterial** cell wall.

3. Hydrolase enzymes mediate particular subsets of transfer reactions in which moieties are...

...which is then available for reuse as the lipid carrier for intermediates 27
involved in **bacterial** cell wall biosynthesis. The topical antibacterial agent bacitracin inhibits the diphosphatase process by sequestering the ...dazoxiben and pirmagrel. A third example of an isomerase is alanine racernase, a soluble, monomeric **bacterial** enzyme that produces D-alanine for incorporation into the cell wall. A fourth example of...

...agents, in particular the quinolones, which inhibit the alpha2beta2 tetrameric topoisomerase II (DNA gyrase) in, **bacterial** cells, and also etoposide, and teniposide, which inhibit the mammalian topoisomerase 11 enzyme.
6. Ligase...

...mediates the ATP-dependent condensation of two D-alanine subunits as an early step in **bacterial** cell wall biosynthesis.

Nearly all known enzymes are proteins. As is true for all proteins... disease states include, but are not limited to, treatment of a mammal afflicted with pathogenic **bacteria** , in particular staphylococci (methicillin sensitive and ...to inhibit gastric acid secretion as described in U.S.

Patent 4,255,43 1.

Dihydrofolate reductase
Anti-leukemia activity is monitored using L 1 21 0 leukemia according to the method...and Carboxyl Groups
Bacitracin is an antibacterial antibiotic that inhibits an enzymatic process involved in **bacterial** cell wall biosynthesis. Bacitracin is a widely utilized animal growth promoter and an important component...

...antibacterial ointments. Bacitracin is effective against a subset of both Gram-positive and Gram-negative **bacteria** in vitro, and it has recently shown promising activity against vancomycin-resistant Enterococcus faecium in...isocarboxazid tranvicypromine. selegifine
(1 3.6) Depression
Dihydrofolate redUCt2se Anti-parasite Chloroguanide. pyrimeLhamme
(microbial) Anti- **bacterial** Trimethoprim
(1 1.3)
DihydrofOl2te reductase Monomer Anti-cancer lvlethotrexate
(1 1.3) Psoriasis
Trypanathione **Dihydrofolate reductase** In vitro Synthetic analoques of trimethoprim were tested
%4 inhibitory effects on protozoan and mammalian
iW **dihydrofolate reductase** using standard analytica
methods
Fn
CD
6-Phosphogluconate In vitro Inhibitors of enzyme activity tested...that bind
M 80
tD (PBP 1-6) PBPs and block cell wall synthesis by **bacteria** ,
were studied

r
M
Transglycosylase In vitro The inhibition of cell wass synthesis was studiec...

...of dihydropteroate synthase by
sulfanilanifides with 3',5'-halogen substitutions
Fn evaluated
CD
D,D- **carboxypeptidase** in vitro Inhibition of enzyme, expressed by
Ochrobactru
(PBP 3-7) anthropi studied
Table 2...racemase In vitro Inactivators of alanine racemase were evaluated
cultures of Gram positive and negative **bacteria**
M
C
W
U)
I Prostacyclin synthase In vitro The effect of enzyme inhibition on...

...effects of inhibitors of cy1cas
were tested
DNA gyrases In vitro Effect of inhibitors, of **bacterial** gyrases, was studied in vitro using time-kill assays 39(12):282
Topoisomerase 11 In...

Claim
... the enzyme is acrosin, the figand cannot be a benzamidine;
when the enzyme is a **bacterial** transglycosylase, the figand cannot be a glycopeptide; when the enzyme is **bacterial** DNA gyrase, the figand cannot be a quinolone;
when the enzyme is thrombin, the ligand...claim 12, wherein the method is chosen from treatment of a mammal afflicted with pathogenic **bacteria** , psoriasis, multiple sclerosis, rheumatoid arthritis, insulindependent diabetes, breast cancer and prostate cancer, disease states related...
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